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Reardon, David A ; Weller, Michael

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Pseudoprogression, Fact or Wishful Thinking in Neuro-Oncology?

David A. Reardon, M.D.

Clinical Director, Center for Neuro-Oncology

Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School

450 Brookline Avenue, D2134

Boston, MA 02215-5450

Telephone: 617-632-2166

Facsimile: 617-632-4773

Email: David_reardon@dfci.harvard.edu

Michael Weller, M.D.

Chairman
Department of Neurology & Brain Tumor Center
University Hospital & University of Zurich
Frauenklinikstrasse 26
CH-8091 Zürich
Tel. +41 44 255 5500
Fax +41 44 255 4507
E-Mail michael.weller@usz.ch

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Interest in the phenomenon of pseudoprogression has rekindled in oncology with the development of immunotherapeutics for many cancers including those involving the central nervous system. Pseudoprogression refers primarily to imaging changes that mimic progressive tumor, but are due to other etiologies that most commonly include inflammation related to therapy. Ramifications for patients and clinicians associated with failure to identify pseudoprogression are substantive and include premature discontinuation of an effective therapy and overestimating the efficacy of a subsequent therapy. The latter may generate misleading results for uncontrolled phase II trials evaluating salvage therapies. Among patients with glioma, including glioblastoma, the most common and difficult to treat type of glioma, pseudoprogression has been reported in up to 30% of patients following radiation combined with temozolomide chemotherapy (RT/TMZ) with most cases noted within 3 months, although delayed cases have been described.[1] Careful consideration of timimg of reference scans and of all interventions in between two MRI scans is required to arrive at this diagnosis. Pseudoprogression can be accompanied by new or worsened neurologic deficits, but many reports note minimal neurologic changes despite disproportionately worsened imaging findings. Pseudoprogression may develop more frequently among patients with a methylated O^6-methylguanine DNA methyltransferase (*MGMT*) promoter,[2] reflecting the enhanced sensitivity of such tumors to TMZ, but this link has not been confirmed. Advanced magnetic resonance imaging sequences such as diffusion and perfusion imaging, and various metabolic imaging modalities including positron emission tomography and spectroscopy, may provide insight into whether progressive imaging findings reflect true versus pseudo progression,[3] but none are definitive. Most patients in this situation undergo close follow-up imaging while continuing treatment, given that pseudoprogression ultimately stabilizes whereas true progression steadily worsens. Surgery can be informative, but biopsies should be interpreted cautiously as sampling artifact may not accurately account for heterogeneity of histopathologic changes. Of note, continuation of treatment despite suspected pseudoprogression precludes distinctions between “true” pseudoprogression and delayed treatment response.

The Radiologic Assessment in Neuro-Oncology (RANO) criteria were drafted to provide guidance for clinicians confronted with pseudoprogression and to standardize how this

situation is handled in clinical trials.[4] RANO specifies that progressive disease can not be determined within three months of completing concomitant RT/TMZ unless confirmed surgically or by new enhancing disease outside the radiation field. Survival is better for patients with pseudoprogression compared to those with early true progression, but is comparable to patients without pseudoprogression or early true progression.[5]

In the current immune-oncology era, there is concern that robust immunologic intratumoral infiltrates could lead to pseudoprogressive imaging findings. In addition, progressive imaging changes may reflect initial true tumor progression that ultimately becomes controlled by a delayed immune response. The immune-related Response Criteria (irRC) were generated to address the possibility of pseudoprogression, including the appearance of new lesions following immunotherapy.[6] Specifically, the irRC criteria call for immunotherapy continuation with follow-up imaging to confirm progression. Among 227 patients with advanced melanoma treated with the CTLA-4 inhibitor ipilimumab, 10% of patients who met WHO criteria for tumor progression demonstrated evidence of subsequent therapeutic benefit when assessed using irRC. With the widespread use of immune checkpoint inhibitors, the frequency of pseudoprogression appears highest in advanced melanoma (3-16%), but is lower in other solid tumors (1-9%).[7] Of note, the frequency and kinetics of pseudoprogression for other immunotherapy treatments such as vaccines or adoptive T cell agents, as well as for the growing number of combinatorial regimens, remains undefined. Importantly, irRC considerations have been incorporated in regulatory guidance materials.[8,9]

Analogous to the irRC, the Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria provide guidance regarding management of possible pseudoprogression among patients with primary and metastatic brain tumors undergoing immunotherapy.[10] iRANO empirically stipulates a three month window for confirmation of progression on follow-up imaging, and further advises that progressive imaging changes beyond six months after immunotherapy initiation are more likely true tumor progression. To date, few neuro-oncology trials evaluating immunotherapies have reported outcome. Among these, including phase 3 studies of anti-PD-1 antibody for recurrent glioblastoma[11] and an EGFRvIII peptide vaccine for newly diagnosed patients,[12] minimal therapeutic benefit

has been observed with rare radiographic responses and lack of improved progression-free or overall survival. In the context of such negative outcomes, the meaning and impact of pseudoprogression becomes moot. Nonetheless, across the spectrum of ongoing trials as well as compassionate use of immunotherapeutic agents, anecdotal reports of pseudoprogression are emerging among neuro-oncology patients. Future neuroimaging and histopathologic data are needed to define the biologic basis and potential prognostic significance of pseudoprogression in a disease- and treatment-specific manner. Neuro-oncologists remain hopeful that immunotherapy will have an impact for their patients, and that a better understanding of pseudoprogression may aid in tailoring novel treatment approaches.

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